1,057,612

PATENT SPECIFICATION

NO DRAWINGS

1,057,612

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Int. Cl.:—C 07 d 99/06

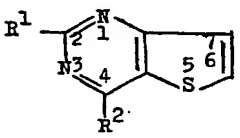
COMPLETE SPECIFICATION

Thieno-Pyrimidines

We, DR. KARL THOMAE, G.M.B.H., a German Body Corporate of Biberach an der Riss, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

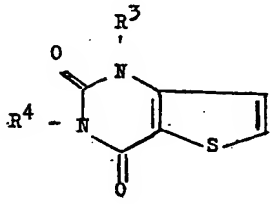
This invention concerns new thieno-[3,2-d]pyrimidines and processes for their preparation.

According to the present invention we provide thieno[3,2-d]pyrimidines of the general formula

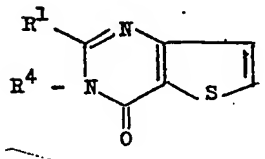


I

and their tautomers of the formulae

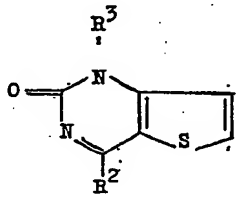


II



III

or



IV

where R^1 is a hydrogen or halogen atom, an alkyl group, an aralkyl group, a free hydroxy group, a hydroxy group substituted by an alkyl, alkenyl, alkoxyalkyl, mono- or dialkyl-aminoalkyl, aryl or aralkyl group, a free mercapto group or a mercapto group substituted by an alkyl group or is an amino group of formula $—NR^5R^6$ wherein R^5 is a hydrogen atom, a free amino group, an alkyl, hydroxyalkyl, alkoxyalkyl, mono- or dialkylaminoalkyl (wherein the dialkylamino group can also be replaced by a saturated heterocyclic ring attached through a nitrogen atom which, if desired, can contain a further heteroatom), amidino, aryl, aralkyl, cycloalkyl or alkenyl group, and R^6 is a hydrogen atom or an alkyl, alkenyl or hydroxyalkyl group, the groups R^5 and R^6 also if desired forming together with the nitrogen atom to which they are attached a saturated heterocyclic ring which, if desired, can be interrupted by a further heteroatom and/or substituted by one or more alkyl groups containing 1—10 carbon atoms or aryl groups;

R^2 is a halogen atom, a free hydroxy group or a hydroxyl group substituted as stated for R^1, a free mercapto group or a mercapto group substituted as stated for R^1 or a free amino group or an amino group substituted as stated for R^1;

[*Price*

R^3 and R^4, which may be the same or different, are hydrogen atoms, alkyl groups, aralkyl or aryl groups, which both may, if desired, be substituted in the aromatic ring by one or more halogen atoms, or alkyl groups containing 1—10 carbon atoms.

The new compounds according to the invention have valuable medicinal properties; in particular they have a cardio-vascular, central-stimulating, diuretic, analgesic, sedative, anti-rheumatic, antiphlogistic, cytostatic, bacteriostatic and fungistatic action, one or the other action being predominent dependent on nature of the substituents R^1 and R^2. The cardio-vascular activity is particularly marked, the action of the compounds widening both the coronary as well as the peripheral blood vessels. The compounds which carry an N-methyl-piperazino group in the 2- or 4-position, are particularly active. Compounds which carry an alkoxy group in the 2-position, have a particularly good sedative activity.

Compounds of especial interest include

4 - pyrrolidino - thieno[3,2 - d]pyrimidine
2,4 - bis(2 - methylmorpholino) - thieno-[3,2 - d]pyrimidine
2 - pyrrolidino - 4 - morpholino - thieno-[3,2 - d]pyrimidine
2 - (4' - methylpiperazinyl - 1') - 4 - isopropylamino - thieno[3,2 - d]pyrimidine and its dihydrochloride
2 - propylamino - 4 - morpholino - thieno-[3,2 - d]pyrimidine
2 - isobutylamino - 4 - morpholino - thieno-[3,2 - d]pyrimidine
2 - isopentylamino - 4 - morpholino - thieno-[3,2 - d]pyrimidine
2 - propylamino - 4 - isopropylamino - thieno-[3,2 - d]pyrimidine
2 - allylamino - 4 - isopropylamino - thieno-[3,2 - d]pyrimidine
2 - methoxy - 4 - morpholino - thieno-[3,2 - d]pyrimidine.

The invention further provides pharmaceutical compositions comprising, as active ingredient, at least one of the compounds according to the invention in association with a pharmaceutical carrier or excipient. The compounds may, for example, be presented in a form suitable for oral, rectal or parenteral administration. Thus, for example, compositions for oral administration may be solid or liquid and may take the form of capsules, tablets, coated tablets, solutions or suspensions, such compositions comprising carriers or excipients conveniently used in the pharmaceutical art. Thus suitable tabletting excipients include lactose, potato and maize starches, talc, gelatine, and stearic and silicic acids, magnesium stearate and polyvinyl pyrrolidone.

For parenteral administration, the carrier or excipient may be a sterile, parenterally acceptable liquid, e.g., pyrogen-free water or an aqueous solution of polyvinyl pyrrolidone, or a parenterally acceptable oil, e.g., arachis oil, contained in ampoules.

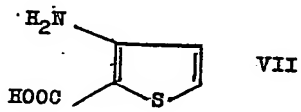
In compositions for rectal administration, the carrier may comprise a suppository base, e.g., cocoa butter or a glyceride.

Advantageously, the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Tablets, coated tablets, capsules, ampoules and suppositories are examples of preferred dosage unit forms according to the invention. Each dosage unit may conveniently contain from 5 to 250 mg., and preferably 10 to 200 mg., of the active ingredient.

Solutions and suspensions may conveniently contain from 0.1 to 5%, and preferably from 0.5 to 2%, of the active ingredient.

The new compounds may be prepared in any convenient way. According to further features of the invention, the compounds may be prepared by the following processes:

1. For the preparation of compounds of formula I, in which R^2 is a free hydroxy group, a free mercapto or a free amino group; reaction of a 3 - aminothiophene - 2 - carboxylic acid of the formula



VII

or a reactive derivative thereof with a compound of the general formula $R^1—CX—NH_2$ in which R^1 has the above-mentioned meanings with the exception of halogen and X is oxygen or sulphur. Reactive derivatives of the 3 - aminothiophene - 2 - carboxylic acid of formula VII include, for example, the esters, amides, thioamides and nitriles. The reaction with the nitrile leads to compounds in which R^2 is a free amino group while the reaction with the thioamide leads to compounds in which R^2 is a free mercapto group; in all other cases compounds are formed in which R^2 is the free hydroxyl group (or the oxo group). Compounds of formula R^1CXNH_2 may, for example, be amides, urea or thiourea. Where urea or thiourea is used, it should be noted that ammonium splits out rather than H_2O or H_2S giving a compound of formula I in which R^1 is a hydroxyl or mercapto group. The reaction may be advantageously effected at elevated temperatures, preferably at temperatures between 100 and 200°C, if desired in the presence of a high-boiling solvent, such as toluene, xylene, and tetrahydronaphthalene.

2. For the preparation of compounds of the general formula I in which R^1 is an alkyl or aralkyl group and R^2 is a free hydroxyl, mercapto or amino group:
Reaction of a 3 - aminothiophene - 2 - carboxylic acid of formula VII, or of a functional derivative thereof with a compound of formula

$$R^1CN$$

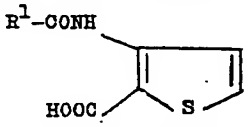
in which R^1 is an alkyl or aralkyl group. Functional derivatives of the carboxylic acid include those given for process 1 and lead to the same derivatives, dependent on the functional derivatives used. The reaction may be effected in the presence of a basic catalyst, preferably in the presence of an alkali metal and in the presence of an inert solvent at elevated temperatures, preferably temperatures of 100° to 200°C. Toluene, xylene and dioxan or an excess of the nitrile employed can be used as solvents.

3. For the preparation of compounds of formula III in which R^1 is a free hydroxyl or mercapto group, and R^4 has the above-mentioned meaning:
Reaction of a 3 - aminothiophene - 2 - carboxylic acid of formula VII, or of a functional derivative thereof with an alkali metal cyanate or thiocyanate or a compound of formula

$$R^4NCX$$

in which R^4 has the above-mentioned meanings and X is oxygen or sulphur. The functional derivatives of the carboxylic acid of formula VII may, for example be esters or amides. The reaction may be effected in the presence of a basic catalyst, preferably a tertiary organic base, at elevated temperatures, advantageously at temperatures above 100°C and advantageously in an inert organic solvent. The initially formed urea or thiourea derivative may then be ring-closed e.g. by boiling with dilute alkali.

4. For the preparation of compounds of formula III in which the group R^4 has the above-mentioned meanings, and R^1 is a hydrogen atom, an alkyl or aralkyl group or a free or substituted amino group:
Reaction of an acylated 3 - aminothiophene - 2 - carboxylic acid of formula



(in which R^1 is a hydrogen atom, an alkyl or aralkyl group or a free or substituted amino group) or an ester thereof, with an amine of formula

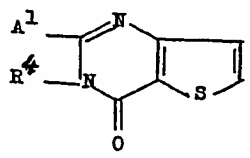
$$R^4NH_2$$

in which R^4 has the above-mentioned meaning, and subsequent ring closure of the amide so formed with a dehydrating agent. The reaction with the amine of formula R^4NH_2 may be effected at elevated temperatures, preferably at temperatures between 100 and 200°C, and advantageously in an inert solvent, for example in an aromatic hydrocarbon or in an excess of the amine reactant. The amide so formed may then be treated, advantageously without isolation and in the same solvent, with a dehydrating agent, advantageously with a phosphorus halide and at elevated temperatures, preferably at temperatures above 100°C.

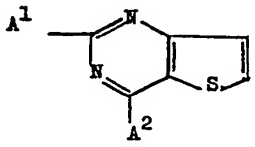
If compounds are obtained by processes 1—4 in which R^1 and/or R^2 are free hydroxyl groups, these can, if desired, be replaced according to known methods by halogen atoms, for example by heating with a phosphorus oxyhalide.

The 3 - aminothiophene - 2 - carboxylic acids of formula VII used in processes 1—5 as starting materials, are known from British Patent Specification 837,086 or can be prepared according to the processes there described.

5. For the preparation of compounds of formulae I, III and IV, in which the groups R^1 and R^2 have the above-mentioned meanings with the exception of halogen atoms: reaction of a compound of formula

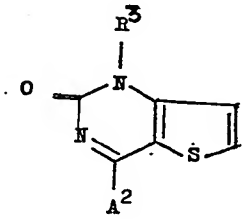


XI A



XI

or



XI B

(in which R^3 and R^4 have the given meanings and one of the groups A^1 and A^2 is a halogen atom, a free mercapto group or a mercapto group substituted by an alkyl group having 1—10 carbon atoms and the

other of the groups A^1 and A^2 (where present) is either a halogen atom, a free mercapto group or a mercapto group substituted by an alkyl group having 1—10 carbon atoms or has one of the other meanings given above for R^1 and R^2) with compounds of formula

$$R^1H \text{ or } R^2H,$$

in which R^1 and R^2 have the above-mentioned meanings with the exception of hydrogen atoms, halogen atoms or alkyl or aralkyl groups.

If according to this process, compounds are to be prepared, in which R^1 and R^2 represent the same group, one starts from a compound of formula IX in which both groups A^1 and A^2 are a halogen atom or a free or alkyl-substituted mercapto group, and reacts this compound with a least a double molar quantity of the compound $R^1H(=R^2H)$. If compounds with different groups R^1 and R^2 are to be prepared, either the group A^2 in compound XI can first be exchanged for the group R^2, and then the group A^1 for the group R^1, or a compound of formula XI may be used as starting substance in which one of the groups A^1 or A^2 already has the meaning of R^1 or R^2, with the exception of a halogen atom or of a free or alkyl-substituted mercapto group.

The reaction is effected advantageously in the presence of an inert organic solvent at temperatures between ambient temperature and 200°C; if A^1 and/or A^2 represent a halogen atom, the presence of a hydrogen halide-binding agent is advisable, for example, an inorganic or tertiary organic base; if R^1 and/or R^2 represents a group of formula $-NR^5R^6$ an at least molar excess of this compound can be used as acid-binding agent. A further excess of this amine can also be used as solvent.

The reaction temperature depends on the reactivity of the reaction components. In general, the exchange of a halogen in the 4-position for one of the given groups may take place in the presence of a hydrogen halide-binding agent at room temperature or a moderately elevated temperature, whilst the exchange of a halogen atom in the 2-position or of a mercapto group in the 2- or 4- position, for a group of formula NR^5R^6 takes place only at temperatures between 70 and 200°C. When using a low boiling solvent or a compound of formula R^1H or R^2H with a low boiling point, the reaction is carried out preferably in a closed vessel.

If R^1 and/or R^2 are to be free or substituted hydroxyl or mercapto groups, one starts preferably from a compound of formula XI in which the exchangeable groups A^1 and/or A^2 are halogen atoms. If a compound of formula I or III, in which R^1 is an alkyl or aralkyl group, is required one must start from a compound of formula XI in which A^1 already has this meaning.

The compounds of formula XI used as starting substances for the process 5, can be obtained according to the processes 1—4 of the present Application or by a further conversion of products so obtained. Compounds in which A^1 and/or A^2 are halogen atoms, can be obtained in the manner mentioned above by halogenation of compounds in which R^1 and/or R^2 are free hydroxyl groups.

Compounds in which A^1 and/or A^2 are free mercapto groups, can either be obtained according to processes 1—5 or by reaction of compounds in which R^1 and/or R^2 are halogen atoms, with alkali metal hydrogen sulphides or with thiourea according to known methods. Finally, they can also be prepared from the corresponding hydroxy compounds by reaction with phosphorus pentasulphide, according to conventional methods.

Compounds in which A^1 and/or A^2 are alkyl thio groups may be prepared from the corresponding halogen compounds by reaction with an alkali metal salt of an alkyl mercaptan or, from the corresponding compounds which R^1 and/or R^2 are free mercapto groups, by alkylation according to conventional methods, for example by means of alkyl halides.

If, according to the processes 1—5, compounds of formula II, III and IV are obtained in which R^3 and/or R^4 are hydrogen atoms, these can, if desired, be converted, e.g. according to conventional methods, into compounds in which R^3 and/or R^4 are alkyl or aralkyl groups, for example by means of the corresponding alkyl or aralkyl halides or by means of dimethyl sulphate.

If, according to processes 1—5, compounds are obtained in which the groups R^1 and/or R^2 are free hydroxyl, free mercapto or free amino groups (which nearly always applies, for example, to R^2) these can, if desired, subsequently be converted, e.g. by conventional methods, into the substituted hydroxyl, mercapto or amino groups given in the definitions of R^1 and R^2, for example by reaction with reactive esters of the corresponding alcohols, especially with the halides or sulphates. Aryl groups cannot be introduced in this manner.

Compounds of formulae I—IV which contain a basic group can, if desired, subsequently be converted into their acid addition salts with physiologically compatible inorganic or organic acids, e.g. by conventional methods such as reaction with acids, for example hydrochloric acid, sulphuric acid, phosphoric acid, succinic acid, tartaric acid, citric acid, maleic acid or fumaric acid. Compounds of formulae I, III and IV in which R^1 and/or R^2 are free hydroxyl or mercapto groups, can, if desired, sub-

sequently be converted into their alkali salts, e.g. by conventional methods such as reaction with alkali.

In order that the invention may be better understood, the following Examples are given by way of illustration only:—

EXAMPLE 1

4 - Hydroxy - thieno[3,2 - d]pyrimidine

4 g. (0.025 mol) of 2 - methoxycarbonyl - 3 - amino - thiophene and 10 ml. (0.25 mol) of formamide are heated for 1 hour at 200°C. Crystals separate from the clear solution on cooling, and are washed with formamide and recrystallised from ethanol.

M.pt. = 218—220°C.
Yield: 2.6 g. (68% of theory)

$C_6H_4N_2OS$	Calc.:	C 47.36	H 2.65	N 18.41	
(M.W. = 152.18)	Found:	37.45	2.76	18.18	

EXAMPLE 2

2,4 - Dihydroxy - thieno[3,2 - d]-pyrimidine

1.6 g. (0.01 mol) of 2 - methoxycarbonyl - 3 - amino - thiophene and 3 g. (0.05 mol) of urea are thoroughly mixed and heated for 2 hours at 200°C. A clear brown melt is formed which solidifies on cooling. The product is dissolved in warm N NaOH, and the solution is decolourised with charcoal and acidified with 2N HCl.

The precipitated crystalline product is filtered off with suction and recrystallised from water.

M.pt. > 300°C.
Yield: 1.2 g. (72% of theory)

$C_6H_4N_2O_2S$	Calc.:	C 42.84	H 2.40	N 16.66	
(M.W. = 168.18)	Found:	42.75	2.57	16.82	

EXAMPLE 3

2 - Methyl - 3 - (o - tolyl) - 4 - oxo - 3,4 - dihydrothieno[3,2 - d]pyrimidine

5.6 g. (0.03 mol) of 2 - carboxy - 3 - acetamido - thiophene and 3.2 g. (0.05 mol) of *o* - toluidine are heated in 250 ml of absolute toluene for 3 hours under reflux. 2.75 g. (0.02 mol) of phosphorus trichloride are then added dropwise and the reaction mixture is refluxed for 3 further hours.

The cooled reaction mixture is extracted with 100 ml. of 10% sodium hydroxide solution, and the organic phase is separated off, washed neutral with water and dried over sodium sulphate.

The toluene is distilled off, and a viscous residue remains which crystallises after some time. It is recrystallised from ethyl acetate.

M.pt. = 128—129°C
Yield: 4.4 g. (57% of theory)

$C_{14}H_{12}N_2OS$	Calc.:	C 65.60	H 4.72	S 12.51	
(M.W. = 256.33)	Found:	65.70	4.79	12.47	

a) 2 - Methyl - 3 - (*p* - chlorophenyl) - 4 - oxo - 3,4 - dihydrothieno[3,2 - d]pyrimidine is prepared similarly from 2 - carboxy - 3 - acetamido - thiophene and *p* - chloroaniline;

M.p.t = 223—225°C. (from ethyl acetate.)

EXAMPLE 4

4 - Chloro - thieno[3,2 - d]pyrimidine

7.6 g. (0.05 mol) of 4 - hydroxy - thieno[3,2 - d]pyrimidine and 50 ml. of phosphorus oxychloride are heated for 4 hours under reflux, yielding a clear solution. The excess of phosphorus oxychloride is taken off *in vacuo*, and the oil remaining is decomposed with ice-water and extracted with chloroform. The organic phase is washed neutral with water and dried over sodium sulphate. The solid residue obtained after distillation of the solvent is recrystallised from benzene.

M.pt. = 125—126°C.
Yield: 5.4 g. (63% of theory)

$C_6H_3ClN_2S$	Calc.:	C 42.24	H 1.77	Cl 20.79	
(M.W. = 170.63)	Found:	42.40	1.81	20.65	

In the same manner the following compound may be prepared:

a) 2,4 - Dichloro - thieno[3,2 - d]pyrimidine from 2,4 - dihydroxy - thieno[3,2 - d]-pyrimidine and phosphorus oxychloride;
M.pt. = 141—142°C (from ethanol).

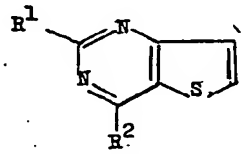
EXAMPLE 5

2 - Chloro - 4 - morpholino - thieno-[3,2 - d]pyrimidine

200 ml. of absolute ethanol are added to 5.1 g. (0.025 mol) of 2,4 - dichloro - thieno-[3,2 - d]pyrimidine. 4.8 g. (0.055 mol) of morpholine are added to the resulting suspension with vigorous stirring and cooling to 20°C. A clear solution is formed from which crystals separate after a short time. The reaction mixture is stirred for two further hours at room temperature.

The product is filtered off with suction, washed with water and ethanol, and recrystallised from methyl ethyl ketone.

The following thieno[3,2 - d]pyrimidines of the formula



can be prepared similarly:

	R^1	R^2	m.p. °C.
a)	Cl	2-methyl-morpholino	169 — 171 (ethanol)
b)	Cl	piperidino	130 — 131 (methanol)
c)	Cl	pyrrolidino	179 — 180 (ethanol)
d)	Cl	C_4H_9NH	94 — 95 (methanol/water 1:1)
e)	Cl	$(CH_3)_2CHNH$	140 — 142 (ethanol)
f)	Cl	$(CH_3)_2N$	166 — 168 (ethanol)
g)	Cl	$HOCH_2CH_2NH$	206 — 207 (ethanol)
h)	Cl	$(HOCH_2CH_2)_2N$	144 — 145 (ethanol)
i)	Cl	$HOCH_2CH_2N(CH_3)$	179 — 180 (ethanol)
j)	Cl	$C_6H_5CH_2CH_2NH$	128 — 129 (methanol)
k)	Cl	H_2N	273 — 275 (ethanol)
l)	Cl	ethylene-imino	118 (methanol)
m)	Cl	$HN{=}C(NH_2).NH$	256 — 258 (butanol)

EXAMPLE 6

2 - Chloro - 4 - ethoxy - thieno[3,2 - d]-pyrimidine

A solution of 0.5 g. (0.22 g. atom) of sodium in 30 ml. of absolute ethanol is added with stirring and cooling to a suspension of 4.1 g. (0.022 mol) of 2,4 - dichloro - thieno[3,2 - d]pyrimidine in 80 ml. of absolute ethanol so that the internal temperature does not exceed 25°C.

An almost clear solution is formed from which crystals separate after a short time. The reaction mixture is stirred for 3 further hours at room temperature, and then filtered with suction, and the crystals are washed with water and ethanol and recrystallised from ethanol.

M.pt. = 137—138°C.
Yield: 4.1 g. (95% of theory)

$C_8H_7ClN_2OS$	Calc.:	C 44.75	H 3.29	S 14.93
(M.W. = 211.68)	Found:	44.88	3.38	14.98

EXAMPLE 7

2,4 - Dimorpholino - thieno[3,2 - d] - pyrimidine

4.1 g (0.02 mol) of 2,4 - dichloro - thieno-[3,2 - d]pyrimidine and 20 ml. of morpholine are mixed at room temperature.

An exothermic reaction occurs and a clear solution is formed from which crystals separate immediately. The reaction mixture is heated for one further hour under reflux, cooled and poured into water. The precipitated product is filtered off with suction, washed with water, and recrystallised from ethanol.

M.pt. = 145—147°C.
Yield: 4.3 g. (70% of theory)

$C_{14}H_{18}N_4O_2S$	Calc.:	C 54.88	H 5.92	N 18.29
(M.W. = 306.39)	Found:	54.90	6.16	18.40

EXAMPLE 8

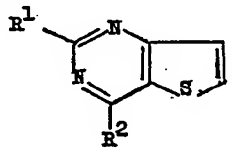
2 - Diethanolamino - 4 - piperidino - thieno[3,2 - d]pyrimidine

3.2 g. (0.0125 mol) of 2 - chloro - 4 - piperidino - thieno[3,2 - d]pyrimidine and 10 ml. of diethanolamine are heated for 4 hours at 150°C. After cooling, the clear solution is poured into water. An oil separates and crystallises after a short time. The reaction product is filtered off with suction, washed with water, and recrystallised from 70% methanol.

M.pt. = 83—84°C.
Yield: 3.0 g. (75% of theory)

$C_{15}H_{22}N_4O_2S$	Calc.:	C 55.99	H 6.88	S 9.95
(M.W. = 322.44)	Found:	55.70	6.92	10.00

According to the methods described in Examples 7 and 8, the following basically substituted thieno[3,2 - d]pyrimidines of the general formula



can be prepared:

	R^1	R^2	m.p. °C.	prepd. acc. Ex.
a)	H	morpholino	136—138 (methanol)	7
b)	H	2-methyl-morpholino	118—120 (ethanol)	7
c)	H	pyrrolidino	143—144 (methanol)	7
d)	H	C_3H_7NH	85— 86 (acetone)	7
e)	H	$(CH_3)_2CHNH$	202—204 (ethanol)	7
f)	H	$CH_2=CHCH_2NH$	116—118 (acetone)	7
g)	H	$(C_2H_5)_2N$	95— 96 (acetone)	7
h)	H	$HOCH_2CH_2NH$	149—150 (ethanol)	7
i)	H	$(HOCH_2CH_2)_2N$	164—165 (ethanol)	7

	R^1	R^2	m.p. °C.	prepd. acc. Ex.
j)	H	$HOCH_2CH_2N(CH_3)$	148—149 (ethanol)	7
k)	H	cyclohexylamino	178—179 (ethanol)	7
l)	H	$C_6H_5CH_2NH$	154—155 (ethanol)	7
m)	H	$C_6H_5(CH_2)_2NH$	205—206 (methyl ethyl ketone)	7
n)	2-methylmorpholino	2-methylmorpholino	86— 87 (petrol)	7
o)	pyrrolidino	pyrrolidino	161—162 (ethanol)	7
p)	$HOCH_2CH_2NH$	$HOCH_2CH_2NH$	144—146 (methanol)	7
q)	$C_6H_5CH_2NH$	$C_6H_5CH_2NH$	150—151 (ethanol)	7
r)	$C_6H_5(CH_2)_2NH$	$C_6H_5(CH_2)_2NH$	65— 66 (ethanol)	7
s)	morpholino	2-methylmorpholino	103—104 (ethanol)	8
t)	morpholino	pyrrolidino	174—176 (ethanol)	8
u)	morpholino	C_4H_9NH	118—119 (methanol)	8
v)	morpholino	$(CH_3)_2CHNH$	156—157 (methanol)	8
w)	morpholino	$(CH_3)_2N$	122—123 (methanol)	8
x)	morpholino	$HOCH_2CH_2NH$	145—147 (methanol)	8
y)	morpholino	$(HOCH_2CH_2)_2N$	130—131 (methanol)	8
z)	morpholino	$HOCH_2CH_2N(CH_3)$	126—127 (methanol)	8
aa)	morpholino	$C_6H_5(CH_2)_2NH$	174—175 (ethanol)	8
ab)	2-methylmorpholino	morpholino	109—110 (methanol)	8
ac)	2-methylmorpholino	morpholino	161—163 (methanol)	8
ad)	piperidino	$(HOCH_2CH_2)_2N$	85— 86 (70% methanol)	8
ae)	piperidino	$HOCH_2CH_2N(CH_3)$	93— 94 (ether)	8
af)	pyrrolidino	morpholino	118—119 (ethanol)	8
ag)	pyrrolidino	$(CH_3)_2N$	141—142 (methanol)	8
ah)	$HOCH_2CH_2N(CH_3)$	piperidino	74— 75 (ether)	8

	R^1	R^2	m.p. °C.	prepd. acc. Ex.
ai)	H_2N	H_2N	196—198 (acetone)	7
aj)	C_3H_7NH	C_3H_7NH	76— 78 (petroleum ether)	7
ak)	$(CH_3)_2CHNH$	$(CH_3)_2CHNH$	87— 89 (petrol)	7
al)	β-morpholino-ethylamino	H_2N	207—208 (methanol)	8
am)	morpholino	H_2N	183—184 (ethanol)	8
an)	morpholino	ethyleneimino	163—164 (methanol)	8
ao)	β-morpholino-ethylamino	pyrrolidino	133—134 (acetone)	8
ap)	piperidino	morpholino	108—109 (methanol)	8
aq)	piperidino	$(CH_3)_2CHNH$	101—103 (ethanol)	8
ar)	4′-methyl-piperazinyl-1′	morpholino	120—121 (ether)	8
as)	4′-methyl-piperazinyl-1′	pyrrolidino	175—176 (acetone)	8
at)	4′-methyl-piperazinyl-1′	H_2N	194—195 (acetone)	
au)	4′-methyl-piperazinyl-1′	C_4H_9NH	92— 94 (petrol)	8
av)	4′-methyl-piperazinyl-1′	C_2H_5NH	100—102 (ether)	8
aw)	4′-methyl-piperazinyl-1′	C_3H_7NH	113—114 (hexane)	8
ax)	4′-methyl-piperazinyl-1′	$CH_2=CHCH_2NH$	105—106 (hexane)	8
ay)	4′-methyl-piperazinyl-1′	$(CH_3)_2CHCH_2NH$	133—134 (hexane)	
az)	4′-methyl-piperazinyl-1′	$(CH_3)_2CHCH_2CH_2NH$	124—125 (hexane)	8
ba)	pyrrolidino	H_2N	250—252 (ethanol)	8
bb)	cyclohexylamino	morpholino	82— 83 (acetone)	8
bc)	C_6H_5NH	morpholino	180—181 (ethanol)	8
bd)	$C_6H_5CH_2NH$	morpholino	142—143 (ethanol)	8
be)	$C_6H_5CH_2CH_2NH$	morpholino	98— 99 (acetone)	8
bf)	C_2H_5NH	pyrrolidino	173—174 (ethanol)	8

	R^1	R^2	m.p. °C.	prepd. acc. Ex.
bg)	C_3H_7NH	morpholino	106—107 (ether)	8
bh)	C_3H_7NH	pyrrolidino	131—132 (acetone)	8
bi)	C_3H_7NH	$(CH_3)_2CHNH$	108—110 (petroleum ether)	8
bj)	C_4H_9NH	morpholino	112—114 (methanol)	8
bk)	C_4H_9NH	pyrrolidino	124—125 (acetone)	8
bl)	C_4H_9NH	H_2N	101—103 (benzene)	8
bm)	$(CH_3)_2CHNH$	morpholino	131—133 (ether)	8
bn)	$(CH_3)_2CHNH$	pyrrolidino	123—124 (ethanol)	8
bo)	$(CH_3)_2CHNH$	H_2N	138—139 (benzene)	8
bp)	$(CH_3)_2CHCH_2NH$	morpholino	93— 94 (ether)	8
bq)	$(CH_3)_2CHCH_2NH$	pyrrolidino	133—134 (acetone)	8
br)	$(CH_3)_2CHCH_2NH$	H_2N	132—134 (benzene)	8
bs)	$(CH_3)_2CHCH_2CH_2NH$	morpholino	89— 90 (ether)	8
bt)	$(CH_3)_2CHCH_2CH_2NH$	pyrrolidino	117—119 (acetone)	8
bu)	$(CH_3)_2CHCH_2CH_2NH$	H_2N	109—111 (acetone)	8
bv)	$CH_2=CHCH_2NH$	$(CH_3)_2CHNH$	103—105 (petrol)	8
bw)	$(CH_2=CHCH_2)_2N$	pyrrolidino	92— 94 (ethyl acetate)	8
bx)	$(CH_3)_2N$	morpholino	103—104 (ether)	8
by)	$(CH_3)_2N$	pyrrolidino	171—172 (acetone)	8
bz)	$(CH_3)_2N$	H_2N	174—175 (methanol)	8
ca)	$(C_2H_5)_2N$	morpholino	62— 63 (ethanol)	8
cb)	$(C_2H_5)_2N$	pyrrolidino	105—107 (methanol)	8
cc)	$(C_2H_5)_2N$	$(CH_3)_2CHNH$	110—111 (petroleum ether)	8
cd)	$(C_2H_5)_2N$	$HOCH_2CH_2NH$	99—100 (methanol)	8
ce)	$HOCH_2CH_2NH$	morpholino	122—123 (acetone)	8
cf)	$(HOCH_2CH_2)_2N$	morpholino	118—119 (methanol)	8
cg)	$(HOCH_2CH_2)_2N$	pyrrolidino	141—142 (acetone)	8
ch)	$(HOCH_2CH_2)_2N$	$(CH_3)_2CHNH$	97— 99 (methanol)	8

	R^1	R^2	m.p. °C.	prepd. acc. Ex.
ci)	$HOCH_2CH_2N(CH_3)$	morpholino	90— 92 (ether/methanol)	8
cj)	$HOCH_2CH_2N(CH_3)$	pyrrolidino	101—102 (ethyl-acetate)	8
ck)	$HOCH_2CH_2N(CH_3)$	$(CH_3)_2CHNH$	99—100 (acetone)	8
cl)	H_2NNH	morpholino	163—164 (ethanol)	8
cm)	$(CH_3)_2NCH_2CH_2NH$	H_2N	167—168 (acetone)	8
cn)	$CH_3OCH_2CH_2CH_2NH$	morpholino	84— 85 (ether)	8
co)	4'-(Methylpiperazinyl-1')	isopropylamino	105—106 (hexane)	8

EXAMPLE 9

2,4 - Diethoxy - thieno[3,2 - d] - pyrimidine

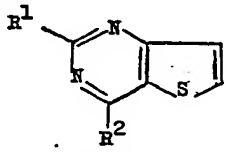
A solution of 1.0 g. (0.044 g. atom) of sodium in 50 ml. of absolute ethanol is added dropwise with stirring at 50°C. to a solution of 4.1 g. (0.02 mol.) of 2,4 - dichloro - thieno[3,2 - d]pyrimidine in 100 ml. of absolute ethanol, and the reaction mixture is refluxed for a further hour.

The precipitated sodium chloride is filtered off with suction and the filtrate is concentrated. Crystals separate and are filtered off with suction, thoroughly washed with water, and recrystallised from ethanol.

M.pt. = 107—108°C.
Yield: 3.7 g. (83% of theory)

$C_{10}H_{12}N_2O_2S$	Calc.:	C	53.55	H	5.39	N 12.49
(M.W. = 224.29)	Found:		53.70		5.48	12.32

The following thieno[3,2 - d]pyrimidines of the formula



can be synthesised in the same manner:

	R^1	R^2	m.p. °C.
a)	H	CH_3O	105—106 (methanol)
b)	H	C_2H_5O	96— 97 (ethanol)
c)	H	$(CH_3)_2CHO$	69— 70 (methanol)
d)	CH_3O	CH_3O	120—121 (methanol)
e)	$(CH_3)_2CHO$	$(CH_3)_2CHO$	62— 63 (acetone)
f)	C_4H_9O	C_4H_9O	47— 49 (methanol)

EXAMPLE 10

2 - Ethoxy - 4 - (2 - methylmorpholino) - thieno[3,2 - d]pyrimidine

5.4 g. (0.02 mol) of 2 - chloro - 4 - (2 - methylmorpholino) - thieno[3,2 - d]pyrimidine and 0.7 g. (0.03 g. atom) of sodium, dissolved in 150 ml. of absolute ethanol, are refluxed for 8 hours. The reaction solution is evaporated *in vacuo*, and the crystalline residue is thoroughly washed with water and recrystallised from 70% aqueous ethanol.

M.pt. = 100—101°C.
Yield: 3.2 g. (57% of theory)

$C_{13}H_{17}N_3O_2S$	Calc.:	C 55.88	H 6.13	S 11.47
(M.W. = 279.37)	Found:	56.00	6.17	11.35

	R^1	R^2	m.p. °C.
(a	CH_3O	morpholino	126—128 (methanol)
b)	CH_3O	2-methylmorpholino	82— 84 (petroleum ether)
c)	CH_3O	pyrrolidino	147—149 (acetone)
d)	CH_3O	H_2N	219—221 (ethanol)
e)	C_2H_5O	morpholino	109—111 (ethanol)
f)	C_2H_5O	pyrrolidino	145—146 (acetone)
g)	C_2H_5O	H_2N	160—162 (acetone)
h)	C_3H_7O	H_2N	131—133 (methanol)
i)	C_4H_9O	2-methylmorpholino	42— 44 (petroleum ether)
j)	$CH_2=CHCH_2O$	$(CH_3)_2CHNH$	105—106 (petroleum ether)
k)	$(CH_3)_2CHO$	morpholino	102—104 (ether)
l)	$(CH_3)_2CHO$	pyrrolidino	141—142 (acetone)
m)	$(CH_3)_2CHO$	$(CH_3)_2CHNH$	141—142 (petroleum ether)
n)	C_6H_5O	morpholino	140—142 (methanol)
o)	$C_6H_5CH_2O$	morpholino	75— 76 (methanol)
p)	$C_2H_5OCH_2CH_2O$	morpholino	80—81 (methanol)
q)	$(CH_3)_2NCH_2CH_2O$	morpholino	73— 74 (petrol)

EXAMPLE 11

2 - Morpholino - 4 - ethoxy - thieno-[3,2 - d]pyrimidine

4.3 g. (0.02 mol) of 2 - chloro - 4 - ethoxy - thieno[3,2 - d]pyrimidine and 10 ml. of morpholine are heated for 4 hours at 100°C. The reaction solution is then poured into water, and an oil separates off and crystallises after a short time. The reaction product is filtered off with suction, washed with water, and recrystallised from methanol.

M.pt. = 105—106°C.
Yield: 3.9 g. (74% of theory)

$C_{12}H_{15}N_3O_2S$	Calc.:	C 54.32	H 5.70	S 12.09
(M.W. = 265.34)	Found:	54.45	5.80	12.21

R^1	R^2	m.p. °C.
a) $HOCH_2CH_2N(CH_3)$	C_2H_5O	85—86 (ether)

EXAMPLE 12

1,3 - Dimethyl - 2,4 - dioxo - 1,2,3,4 - tetrahydro - thieno[3,2 - d]pyrimidine

5.7 g. (0.045 mol) of dimethyl sulphate are added with stirring to a mixture of 1.7 g. (0.01 mol) of 2,4 - dihydroxy - thieno-[3,2 - d]pyrimidine and 12 ml. of 2N - sodium hydroxide solution.

An exothermic reaction occurs and a clear solution is formed, from which crystals rapidly separate.

The crystals are stirred for 15 further hours, filtered off with suction, thoroughly washed with water and ethanol, and recrystallised from ethanol.

M.pt. = 186—187°C.
Yield: 1.7 g. (87% of theory)

$C_8H_8N_2O_2S$	Calc.:	C 48.97	H 4.11	S 16.34
(M.W. = 196.23)	Found:	48.90	4.14	16.20

EXAMPLE 13

4 - Mercapto - thieno[3,2 - d]pyrimidine

3.8 g. (0.025 mol) of 4 - hydroxy - thieno-[3,2 - d]pyrimidine and 6.1 g. (0.077 mol) of phosphorus pentasulphide are refluxed in 60 ml. of absolute pyridine for 4 hours. The resulting clear, dark-brown solution is concentrated *in vacuo* to about half its volume.

An equal volume of water is added, and the mixture is refluxed for one hour and then cooled with ice. The precipitate yellow product is filtered off with suction, washed with water, reprecipitated from sodium hydroxide solution with iced acetic acid, and recrystallised from dimethyl formamide.

M.pt. = >300°C.
Yield: 3.1 g. (74% of theory)

$C_6H_4N_2S_2$	Calc.:	C 42.85	H 2.40	S 38.12
(M.W. = 168.25)	Found:	43.00	2.51	38.20

EXAMPLE 14

4 - Methylthio - thieno[3,2 - d]-pyrimidine

14.2 g. (0.1 mol) of methyl iodide are added with stirring and cooling to a solution of 3.3 g. (0.02 mol) of 4 - mercapto - thieno[3,2 - d]pyrimidine in 30 ml. of 2N - potassium hydroxide solution. The reaction product crystallises out after a short time. It is filtered off with suction, washed with water and recrystallised from ethanol.

M.pt. = 110—111°C.
Yield: 1.9 g. (53% of theory)

$C_7H_6N_2S_2$	Calc.:	C 46.13	H 3.31	S 35.19
(M.W. = 182.27)	Found:	46.25	3.37	34.98

EXAMPLE 15

4 - Hydrazino - thieno[3,2 - d]-pyrimidine

5.1 g. (0.03 mol) of 4 - chloro - thieno-[3,2 - d]pyrimidine are added to a mixture of 50 ml. of ethanol and 50 ml. of 80% hydrazine hydrate. An exothermic reaction occurs, and the resulting solution is then refluxed for one further hour. The solution is cooled, and the crystals separating are filtered off with suction, washed with ethanol and recrystallised from ethanol.

M.pt. = 246—248°C. (decomposition)
Yield: 3.5 g. (70% of theory)

$C_6H_6N_4S$	Calc.:	C 42.36	H 3.64	S 19.30
(M.W. = 166.21)	Found:	43.55	3.74	19.10

EXAMPLE 16

2 - Benzyl - 4 - hydroxy - thieno-[3,2 - d]pyrimidine

4.1 g. (0.18 g. atom) of finely powdered sodium are heated at 85—90°C. in a mixture of 30 ml. of absolute toluene and 60 ml. of absolute benzene. During two hours, a solution of 14.1 g. (0.09 mol) of 2 - methoxycarbonyl - 3 - amino - thiophene in 35 g. (0.3 mol) of benzyl cyanide is added dropwise and the reaction solution is refluxed for 8 further hours. 60 ml. of absolute ethanol are added to the reaction mixture which is then evaporated to dryness. The viscous residue is dissolved in 300 ml. of N sodium hydroxide solution, the resulting solution is three times extracted with toluene, and the aqueous phase is weakly acidified with 2N hydrochloric acid (pH = 5.6).

The precipitate is filtered off with suction, washed with water and recrystallised from dimethyl formamide.

M.pt. $<$ 300°C.
Yield: 7.4 g. (34% of theory)

$C_{13}H_{10}N_2OS$	Calc.:	C 64.44	H 4.16	S 13.24
(M.W. = 242.30)	Found:	64.16	4.28	13.34

EXAMPLE 17

2 - (4' - methyl - piperazinyl - 1') - 4 - isopropylamino - thieno[3,2, - d]-pyrimidine dihydrochloride

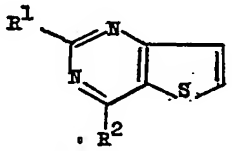
Ethereal hydrogen chloride is added to 1.45 g. (0.005 mol) of 2 - (4' - methyl - piperazinyl - 1') - 4 - isopropylamino - thieno[3,2 - d]pyrimidine dissolved in 50 ml. of absolute ether until the solution is acid to congo-red.

The precipitated hydrochloride is filtered off with suction, washed with absolute ether and recrystallised from absolute ethanol. White crystals of m.pt. 285°C. (decomp.) are obtained.

Yield: 1.6 g. (88% of theory)

$C_{14}H_{23}Cl_2N_5S$	Calc.:	C 46.15	H 6.36	S 8.80
(M.W. = 364.35)	Found:	45.90	6.40	8.83

The following hydrochlorides of the general formula



. x HCl

can be prepared similarly:

	R^1	R^2	m.p. °C.
a)	H	4'-methylpiperazinyl-1'	250—252 (ethanol)
b)	H	ethyleneimino	256—257 (ethanol)
c)	4'-methylpiperazinyl-1'	C_2H_5O	289—290 (ethanol)
d)	C_2H_5NH	C_2H_5NH	228—230 (ethanol-ethyl acetate)
e)	$(CH_3)_2CHCH_2CH_2NH$	$(CH_3)_2CHCH_2CH_2NH$	177—178 (acetone)
f)	$(CH_2=CHCH_2)_2N$	$(CH_2=CHCH_2)_2N$	118—120 (ethyl acetate)
g)	C_3H_7NH	$C_6H_5CH_2CH_2NH$	186—188 (ethanol-ethyl acetate)
h)	$C_5H_{11}NH$	morpholino	185—187 (methyl-ethyl ketone)
i)	$(CH_2=CHCH_2)_2N$	morpholino	173—174 (ethanol) ethyl acetate)
j)	$(CH_3)_2NCH_2CH_2NH$	morpholino	268—270 (butanol)
k)	$(CH_3)_2NCH_2CH_2NH$	$(CH_3)_2CHNH$	115—118 (ethanol-ethyl acetate)
l)	β-morpholinoethylamino	morpholino	275—277 (ethanol)
m)	β-morpholinoethylamino	$(CH_3)_2CHNH$	283—285 (ethanol)
n)	$(CH_3)_2NCH_2CH_2CH_2NH$	morpholino	235—237 (methanol-ethyl acetate)
o)	4'-methylpiperazinyl-1'	2-methylmorpholino	260—261 (ethanol-ethyl acetate)
p)	4'-methylpiperazinyl-1'	piperidino	280 (decomp.) (ethanol)
q)	C_3H_7NH	2-methylmorpholino	205—207 (methyl-ethyl ketone)
r)	$(CH_3)_2CHCH_2CH_2NH$	2-methylmorpholino	184—186 (methyl-ethyl ketone)
s)	$(C_2H_5)_2NCH_2CH_2NH$	morpholino	234—236 (butanol)

EXAMPLE 18

2,4 - Dihydroxy - thieno[3,2 - d]-pyrimidine

A solution of 16.2 g. (0.2 mol) of potassium cyanate in 25 ml. of water is slowly added dropwise with stirring at a temperature of 15—20°C. to a solution of 15.7 g. (0.1 mol) of 2 - methoxycarbonyl - 3 - amino-thiophene in 250 ml. of acetic acid. White crystals separate immediately. The reaction mixture is left for 5 further hours at room temperature and then filtered with suction. The crystals are dissolved in 250 ml. of hot 2N sodium hydroxide solution. This solution is cooled and acidified, and the desired compound precipitates out analysis-pure. It is filtered off with suction, washed with water and dried.

M.pt. > 300°C.

$C_6H_4N_2O_2S$ (M.W. = 168.18) Calc.: C 42.84 H 2.40 N 16.66
Found: 42.87 2.49 16.64

In the same manner the following compound can be prepared:

a) 2 - Mercapto - 4 - hydroxy - thieno-[3,2 - d]pyrimidine from 2 - methoxycarbonyl - 3 - amino - thiophene and potassium thiocyanate;

m.pt. > 300 (from dimethyl formamide)

EXAMPLE 19

2 - Hydroxy - 3 - phenyl - 4 - oxo - 3,4 - dihydrothieno[3,2 - d]pyrimidine

7.8 g. (0.05 mol) of 2 - methoxycarbonyl - 3 - aminothiophene and 23.8 g. (0.2 mol) of phenyl isocyanate are dissolved in 150 ml. of absolute toluene.

2.0 ml. of triethylamine are slowly added, and the reaction solution is refluxed for 8 hours. The solution is then cooled, and the resulting crystals are filtered off with suction, washed with toluene, dried, and heated in 250 ml. of 2N sodium hydroxide solution. The undissolved material is separated, and the solution is cooled and acidified with iced acetic acid. The precipitated compound is filtered off with suction, washed with water and dried.

M.pt. < 300°C.
Yield: 8.0 g. (63% of theory)

$C_{12}H_8N_2O_2S$	Calc.:	C 59.00	H 3.30	N 11.47	
(M.W. = 244.28)	Found:	59.12	3.38	11.34	

EXAMPLE 20

2 - Ethylthio - 4 - hydroxy - thieno-[3,2 - d]pyrimidine

30.0 g. (0.275 mol) of ethyl bromide are slowly added with stirring at 50°C. to a solution of 10.0 g. (0.055 mol) of 2 - mercapto - 4 - hydroxy - thieno[3,2 - d]pyrimidine in 50 ml. of 2N sodium hydroxide solution.

The mixture is then refluxed for 2 hours, cooled, and the clear solution is acidified with iced acetic acid. A crystalline substance precipitates out and is filtered off with suction, washed with water and recrystallised from ethanol.

M.pt. = 201—203°C.
Yield: 9.0 g. (77% of theory)

$C_8H_8N_2OS_2$	Calc.:	C 45.26	H 3.80	S 30.21	
(M.W. = 212.30)	Found:	45.40	3.85	30.03	

EXAMPLE 21

2 - Morpholino - 4 - hydroxy - thieno-[3,2 - d]pyrimidine

7.0 g. (0.033 mol) of 2 - ethylthio - 4 - hydroxy - thieno]3,2 - d]pyrimidine and 50 ml. of morpholine are heated for 10 hours in a bomb at 160°C.

The cooled reaction mixture is poured into water, acidified with iced acetic acid to pH 5 and the precipitated crystals are filtered off with suction and washed with water. The crystals are recrystallised from dimethyl formamide, and white crystals are obtained.

M.pt. = 256—258°C.
Yield: 6.8 g. (87% of theory)

$C_{10}H_{11}N_3O_2S$	Calc.:	C 50.61	H 4.67	
(M.W. = 237.29)	Found:	50.65	4.80	

In the same manner, the following compound can be prepared:

a) 2 - (4' - methyl - piperazinyl - 1') - 4 - hydroxy - thieno[3,2 - d]pyrimidine from 2 - ethylthio - 4 - hydroxy - thieno[3,2 - d]-pyrimidine and N - methyl - piperazine; m.pt. = 225—226°C. (from ethanol).

EXAMPLE 22

2.4 g. (0.01 mol) of 2 - morpholino - 4 - hydroxy - thieno[3,2 - d]pyrimidine and 30 ml. of phosphorus oxychloride are refluxed for 2 hours. A clear solution is obtained. The excess of phosphorus oxychloride is taken off *in vacuo*, and the oily residue is decomposed with ice-water and extracted with chloroform.

The extract is washed neutral with water and dried over sodium sulphate. The chloroform solution is concentrated and a solid substance remains which is recrystallised from ether.

M.pt. = 105°C.
Yield: 2.0 g. (78% of theory)

$C_{10}H_{10}ClN_3OS$	Calc.:	C 46.97	H 3.94	
(M.W. = 255.74)	Found:	46.84	4.03	

In the same manner the following compound can be prepared:

a) 2 - (4' - methyl - piperazinyl - 1') - 4 - chloro - thieno[3,2 - d]pyrimidine from 2 - (4' - methyl - piperazinyl - 1') - 4 - hydroxy - thieno[3,2 - d]pyrimidine and phosphorus oxychloride; m.pt. 87—89°C. (from petroleum ether).

M.pt. = 174—176°C.
Yield: 2.1 g. (72% of theory)

$C_{14}H_{18}N_4OS$	Calc.:	C 57.90	H 6.25	N 19.30
(M.W. = 290.39)	Found:	57.85	6.30	19.37

All compounds described in Examples 7 and 8 can by synthesised in this manner.

EXAMPLE 24

2 - Mercapto - 4 - morpholino - thieno-[3,2 - d]pyrimidine

5.1 g. (0.02 mol) of 2 - chloro - 4 - morpholino - thieno[3,2 - d]pyrimidine and 3.8 g. (0.05 mol) of thiourea are dissolved in 300 ml. of absolute ethanol and refluxed for 15 hours. The solution is cooled and the resulting crystals are filtered off with suction and recrystallised from dimethyl formamide.

M.pt. = 267—269°C.
Yield: 3.4 g. (68% of theory)

$C_{10}H_{14}N_3OS_2$	Calc.:	C 47.41	H 4.38	
(M.W. = 253.35)	Found:	47.25	4.45	

EXAMPLE 23

2 - Morpholino - 4 - pyrrolidino - thieno[3,2 - d]pyrimidine

2.55 g. (0.01 mol) of 2 - morpholino - 4 - chloro - thieno[3,2 - d]pyrimidine and 15 ml. of pyrrolidine are refluxed for 30 minutes. The reaction mixture is cooled, and the precipitated crystals are filtered off with suction, washed with ethanol and recrystallised from ethanol.

The following Examples 25 to 30 illustrate pharmaceutical compositions according to the invention:

EXAMPLE 25

Tablets each containing 100 mg. of 2 - methoxy - morpholino - thieno[3,2 - d]-pyrimidine:

1 tablet contains:	
2 - Methoxy - 4 - morpholino - thieno[3,2 - d]pyrimidine	100.0 mg.
Maize starch	45.0 mg.
Calcium phosphate (secondary)	77.0 mg.
polyvinyl pyrrolidone	6.0 mg.
Magneium tearate	2.0 mg.
	230.0 mg.

Method of preparation:

The active substance, maize starch and calcium phosphate are mixed and granulated with a 15% solution of polyvinyl pyrrolidone in water through a sieve of mesh width 1.5 mm. The granulate is dried at 40°C. and is again ground through the same sieve and mixed with magnesium stearate. Tablets are pressed from the mixture.

Tablet weight: 230 mg.
Die: 9 mm., flat.

EXAMPLE 26

Dragees each containing 25 mg. of 2 - n - propylamino - 4 - isopropylamino - thieno-[3,2 - d]pyrimidine:

1 dragee core contains:	
2 - n - Propylamino - 4 - isopropylamino - thieno[3,2 - d]-pyrimidine	25.0 mg.
Calcium phosphate (secondary)	75.0 mg.
Maize starch	21.0 mg.
Gelatine	4.0 mg.
Talc	4.0 mg.
Magnesium stearate	1.0 mg.
	130.0 mg.

Method of preparation:

The active substance, calcium phosphate and maize starch are mixed and granulated with a 15% solution of gelatine in water through a sieve of mesh width 1.5 mm. The granulate is dried at 40°C. and is ground through a sieve of mesh width 1.0 mm. and mixed with talc and magnesium stearate. Dragee cores are pressed from the mixture.

Core weight: 130 mg.
Die: 7 mm., convex.

The dragee cores thus prepared are covered according to known methods with a dragee coating which consists substantially of sugar and talc. The finished dragees are polished with the aid of beeswax.

EXAMPLE 27

Suppositories each containing 200 mg. of 2,4 - dimorpholino - thieno[3,2 - d]pyrimidine.

1 suppository contains:

2,4 - Dimorpholino - thieno-[3,2 - d] - pyrimidine	200.0 mg.
Suppository base (e.g., *Witepsol W 45)	1550.0 mg.
	1750.0 mg.

*Registered Trade Mark of Chemische Werke Witten. Mixture of triglycerides of naturally-occurring saturated fatty acids of chain length C_{12} to C_{18}.

Method of preparation:

The finely powdered active substance is stirred into the melted suppository base which has been cooled to 37°C., and the suspension is homogenised. The mass is poured into slightly pre-cooled moulds.

Suppository weight: 1.75 g.

EXAMPLE 28

Ampoules each containing 10 mg. of 2 - (4' - methyl - piperazinyl - 1') - 4 - isobutylamino - thieno[3,2 - d]pyrimidine.

1 ampoule contains:

2 - (4' - methyl - piperazinyl - 1') - 4 - isobutylamino - thieno[3,2 - d]pyrimidine	10.0 mg.
Tartaric acid	20.0 mg.
Bidistilled water	ad 2.0 ml.

Method of preparation:

In about one quarter of the required amount of water, tartaric acid and 2 - (4' - methyl - piperazinyl - 1') - 4 - isobutylamino - thieno[3,2 - d]pyrimidine are successively dissolved while protected from light and under a stream of nitrogen. The solution is diluted to the required volume and filtered free of suspended particles.

Filling: into brown 2 ml. ampoules under a stream of nitrogen,

Sterilisation: 30 minutes at 100°C.

EXAMPLE 29

Drop solution containing 10 g. of 2 - (4' - methyl - piperazinyl - 1') - 4 - isobutylamino - thieno[3,2 - d]pyrimidine.

1 ml. of drop solution contains:

2 - (4 - methyl - piperazinyl - 1') - 4 - isobutylamino - thieno[3,2 - d]pyrimidine	10.0 mg.
Tartaric acid	10.0 mg.
Cane sugar	350.0 mg.
Sorbic acid	1.0 mg.
Cocoa essence	50.0 mg.
Ethyl alcohol	0.2 ml.
Polyethylene glycol 600	0.1 ml.
Distilled water	ad 1.0 ml.

Method of preparation:

The sorbic acid is dissolved in alcohol and an equal volume of water is added. The tartaric acid and active substance are dissolved therein (solution 1). The sugar is dissolved in the remaining water (solution 2). Solution 2, polyethylene glycol and cocoa essence are added with stirring to solution 1, and the resulting mixture is filtered through a suitable filter. 1 ml. of drop solution contains 10 mg. of 2 - (4' - methyl - piperazinyl - 1') - 4 - isobutylamino - thieno[3,2 - d]-pyrimidine.

The solution must be prepared, filled and sored under a stream of nitrogen, and protected from white light.

EXAMPLE 30

Gelatine capsules each containing 20 mg. of 2 - isopentylamino - 4 - morpholino - thieno[3,2 - d]pyrimidine.

1 capsule contains:

2 - Isopentylamino - 4 - morpholino - thieno - [3,2 - d]pyrimidine	20.0 mg.
Lactose	60.0 mg.
Talc	20.0 mg.
	100.0 mg.

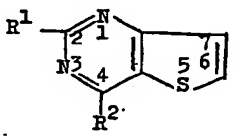
Method of preparation:

The substances are intensively mixed, ground through a sieve of mesh-width 1 mm., and filled into gelatine capsules of a suitable size.

Capsule filling: 100 mg.

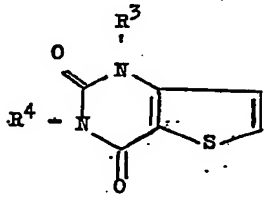
WHAT WE CLAIM IS:—

1. Thieno[3,2 - d]pyrimidines of the general formula

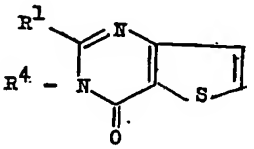


I

and their tautomers of the formulae

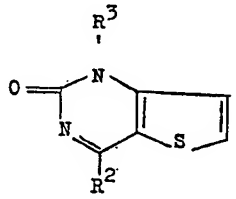


II



III

or



IV

where R^1 is a hydrogen or halogen atom, an alkyl group, an aralkyl group, a free hydroxy group, a hydroxy group substituted by an alkyl, alkenyl, alkoxyalkyl, mono- or di-alkylaminoalkyl, aryl or aralkyl group, or is a free mercapto group, or a mercapto group substituted by an alkyl group or is an amino group of formula $—NR^5R^6$ wherein R^5 is a hydrogen atom, a free amino group, an alkyl, hydroxyalkyl, alkoxyalkyl, mono- or di-alkylaminoalkyl (wherein the dialkylamino group can also be replaced by a saturated heterocyclic ring attached through a nitrogen atom which, if desired, can contain a further heteroatom), amidino, aryl, aralkyl, cycloalkyl or alkenyl group, and R^6 is a hydrogen atom or an alkyl, alkenyl or hydroxyalkyl group, the groups R^5 and R^6 also if desired forming, together with the nitrogen atom to which they are attached, a saturated heterocyclic ring which, if desired, can be interrupted by a further heteroatom and/or substituted by one or more lower alkyl or aryl groups;

R^2 is a halogen atom, a free hydroxyl group or a hydroxyl group substituted as stated for R^1, a free mercapto group or a mercapto group substituted as stated for R^1 or a free amino group or an amino group substituted as stated for R^1;

R^3 and R^4, which may be the same or different, are hydrogen atoms, alkyl groups, aralkyl or aryl groups, which both may, if desired, be substituted in the aromatic ring by one or more halogen atoms, or alkyl groups containing 1—10 carbon atoms.

2. 4 - Pyrrolidino - thieno[3,2 - d] - pyrimidine.

3. 2,4 - Bis(2 - methylmorpholino) - thieno[3,2 - d]pyrimidine.

4. 2 - Pyrrolidino - 4 - morpholino - thieno[3,2 - d]pyrimidine.

5. 2 - (4′ - Methylpiperazinyl - 1′) - 4 - isopropylamino - thieno[3,2 - d]pyrimidine and its dihydrochloride.

6. 2 - Propylamino - 4 - morpholino - thieno[3,2 - d]pyrimidine.

7. 2 - Isobutylamino - 4 - morpholino - thieno[3,2 - d]pyrimidine.

8. 2 - Isopentylamino - 4 - morpholino - thieno[3,2 - d]pyrimidine.

9. 2 - Propylamino - 4 - isopropylamino - thieno[3,2 - d]pyrimidine.

10. 2 - Allylamino - 4 - isopropylamino - thieno[3,2 - d]pyrimidine.

11. 2 - Methoxy - 4 - morpholino - thieno[3,2 - d]pyrimidine.

12. Acid addition salts of the bases claimed in claims 1—11.

13. Hydrochlorides, sulphates, phosphates, succinates, tartrates, citrates, maleates and fumarates of the bases as claimed in any of claims 1—11.

14. Salts with bases of acidic compounds as claimed in claim 1.

15. Alkali metal salts of acidic compounds as claimed in claim 1.

16. Compounds as claimed in claim 1 as herein described.

17. Compounds as claimed in claim 1 substantially as herein described with reference to any of the Examples and Tables.

18. A pharmaceutical composition comprising, as active ingredient, at least one compound as claimed in any of claims 1 to 17 in association with a pharmaceutical carrier or excipient.

19. A composition as claimed in claim 18 in the form of dosage units.

20. A composition as claimed in claim 19 in the form of tablets, coated tablets, capsules, ampoules, or suppositories.

21. A composition as claimed in claim 19 containing from 5 to 250 mg. of active ingredient per dosage unit.

22. A composition as claimed in claim 21 containing from 10 to 200 mg. of active ingredient per dosage unit.

23. A composition as claimed in claim 18 in the form of a solution or suspension.

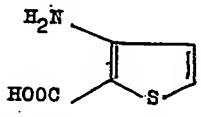
24. A composition as claimed in claim 23 containing from 0.1 to 5% by weight of active ingredient.

25. A composition as claimed in claim 24 containing from 0.5 to 2% of active ingredient.

26. A composition as claimed in claim 18 substantially as herein described.

27. A composition as claimed in claim 18 substantially as herein described in any of Examples 25 to 30.

28. A process for the preparation of compounds of formula I as claimed in claim 1 in which R^2 is a free hydroxyl, mercapto or amino group and R^1, R^3, R^4, R^5 and R^6 have the meanings given in claim 1 wherein a 3 - aminothiophene - 2 - carboxylic and of the general formula



VII

or a reactive derivative thereof is reacted with a compound of the general formula

R^1—CX—NH_2 in which R^1 has the meaning given in claim 1 with the exception of halogen and X is oxygen or sulphur.

29. A process as claimed in claim 28 in which the reactive derivative of the acid of formula VII is an ester, amide, thioamide or nitrile.

30. A process as claimed in claim 28 or claim 29 in which the compound R^1CXNH_2 is an amide, urea or thiourea.

31. A process for the preparation of compounds of the general formula I as shown in claim 1 in which R^1 is an alkyl, aryl or aralkyl group, and R^2 is a free hydroxyl, mercapto or amino group in which a 3 - aminothiophene - 2 - carboxylic acid of the general formula VII shown in claim 28 or a functional derivative thereof is reacted with a nitrile of the general formula R^1CN where R^1 is an alkyl or aralkyl group.

32. A process as claimed in claim 31 in which the reaction is effected in the presence of a basic catalyst.

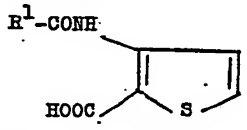
33. A process as claimed in claim 32 in which the basic catalyst is an alkali metal.

34. A process for the preparation of compounds of the general formula III shown in claim 1 (in which R^1 is a free hydroxyl or mercapto group, and R^4 has the meaning given in claim 1 in which a 3 - amino - thiophene - 2 - carboxylic acid of the formula VII shown in claim 28 or a functional derivative thereof is reacted with an alkali metal cyanate or thiocyanate or a compound of the general formula R^4NCX (where R^4 has the meaning given in claim 1 and X is oxygen or sulphur) followed by ring-closure of the product so formed.

35. A process as claimed in claim 34 in which the reaction of the compound VII is effected in the presence of a basic catalyst.

36. A process as claimed in claim 34 and claim 35 in which the ring closure is effected by heating with dilute alkali.

37. A process for the preparation of compounds of general formula III as shown in claim 1 (in which the group R^4 has the meanings given in claim 1 and R^1 is a hydrogen atom, an alkyl or aralkyl group or a free or substituted amino group) in which an acylated 3 - aminothiophene - 2 - carboxylic acid of the general formula



(in which R^1 is a hydrogen atom, an alkyl or aralkyl group or a free or subsituted amino group) or an ester thereof is reacted with an amine of the general formula R^4NH_2 (where R^4 has the meaning given in claim 1) followed by ring-closure of the amide so formed by reaction with a dehydrating agent.

38. A process as claimed in claim 37 in which the dehydrating agent is a phosphorus halide.

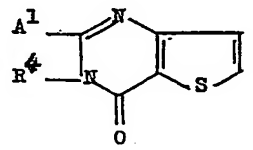
39. A process as claimed in any of claims 28 to 38 which is effected at elevated temperature.

40. A process as claimed in any of claim 28 to 39 which is effected at between 100° and 200°C.

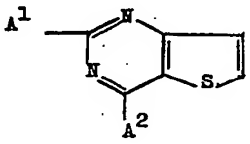
41. A process as claimed in any of claims 28 to 40 in which the reaction is effected in an inert solvent.

42. A process as claimed in any of claims 28 to 41 in which, in order to produce compounds of general formulae I, II, III or IV shown in claim 1 in which R^1 and/or R^2 is a halogen atom, a compound of said general formulae in which R^1 and/or R^2 is a free hydroxyl group is reacted with a phosphorus halide.

43. A process for the preparation of compounds of the general formulae I, III and IV shown in claim 1 in which the groups R^1 and R^2 have the meanings given in claim 1 with the exception of halogen atoms) in which a compound of the general formula

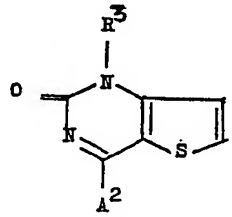


XI A



XI

or



XI B

(in which R^3, R^4, have the meanings given in claim 1 and one of the groups A^1 and A^2, which may be the same or different, is a halogen atom, a free mercapto group or a mercapto group substituted by an alkyl group having 1—10 carbon atoms and the other of the groups A^1 and A^2 (where present) is a halogen atom, a free mercapto group, a mercapto group substituted by an alkyl group having 1—10 carbon atoms or has one of the other meanings given in claim 1 for R^1 and R^2) is reacted with a compound of the general formula R^1H or R^2H in which R^1

and R^2 have the meanings given in claim 1 with the exception of hydrogen or halogen atoms r alkyl or aralkyl groups.

44. A process as claimed in claim 43 in which, where A^1 and/or A^2 is halogen, the reaction is effected in the presence of a hydrogen halide acceptor.

45. A process as claimed in claim 44 in which the hydrogen halide acceptor is an inorganic or tertiary organic base or an excess of the compound R^1H or R^2H if this is a base.

46. A process as claimed in any of claims 43 to 45 in which the reaction is effected in an inert solvent medium or an excess of one of the reactants if this is liquid at the reaction temperature.

47. A process as claimed in any of claims 43 to 46 in which the reaction temperature is between ambient temperature and 200°C.

48. A process as claimed in any of claims 43 to 47 in which a starting compound of formula XI in which A^1 and/or A^2 is halogen is prepared by reaction of a compound of formula I as shown in claim 1 in which R^1 and/or R^2 is a hydroxyl group with a halogenating agent.

49. A process as claimed in any of claims 43 to 47 in which a starting compound of formula XI, XI A or XI B as shown in claim 43 in which A^1 and/or A^2 is a free mercapto group or an alkylthio group is prepared by reaction of a compound of formula I as shown in claim 1 in which R^1 and/or R^2 is a halogen atom with an alkali metal hydrogen sulphide, thiourea or an alkali metal salt of an alkyl mercaptan.

50. A process as claimed in any of claims 28 to 47 in which, in order to produce compounds of formula I, as shown in claim 1 in which R^1 and/or R^2 are substituted hydroxyl, mercapto or amino groups, compounds of formula I in which R^1 and/or R^2 are free hydroxyl, mercapto or amino groups are reacted with a reactive derivative of the corresponding alcohol.

51. A process for the production of compounds of general formulae II, III or IV shown in claim 1 in which R^3 and/or R^4 is an alkyl or aralkyl group in which a compound of formula II, III or IV in which R^3 and/or R^4 is a hydrogen atom is reacted with a reactive derivative of the corresponding alcohol.

52. A process as claimed in claim 50 or claim 51 in which the reactive derivative is a halide or sulphate of said alcohol.

53. A process as claimed in any of claims 28 to 52 in which, in order to form an acid addition salt thereof, a basic product having the formula I, II, III or IV as claimed in claim 1 is reacted with a physiologically compatible organic or inorganic acid.

54. A process as claimed in claim 53 in which the said acid is hydrochloric, sulphuric, phosphoric, succinic, tartaric, citric, maleic or fumaric acid.

55. A process as claimed in any of claims 28 to 52 in which an acidic product having the formula I, III or IV as claimed in claim 1 is reacted with alkali to form a salt therewith.

56. A process as claimed in claim 28 substantially as herein described.

57. A process as claimed in claim 28 substantially as herein described with reference to Example 1 or Example 2.

58. A process as claimed in claim 31 substantially as herein described.

59. A process as claimed in claim 31 substantially as herein described with reference to Example 16.

60. A process as claimed in claim 34 substantially as herein described.

61. A process as claimed in claim 34 substantially as herein described with reference to Example 18.

62. A process as claimed in claim 37 substantially as herein described.

63. A process as claimed in claim 37 substantially as herein described with reference to Example 3.

64. A process as claimed in claim 43 substantially as herein described.

65. A process as claimed in claim 43 substantially as herein described with reference to any of Examples 5 to 11, 15, 21, and 23.

66. Compounds as claimed in claim 1 whenever prepared by a process as claimed in any of claims 28 to 65.

For the Applicants,
FRANK B. DEHN & CO.
Chartered Patent Agents,
Imperial House,
15—19, Kingsway,
London, W.C.2.

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